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DOCKET NO. 17282CPA(BOT)  
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of

Sachs et al

U.S. Patent 6,776,990B2

Serial No: 09/288,326

Issued: August 17, 2004

Filed: April 8, 1999

Group Art Unit: 1644

Examiner: K. Clemens

For: METHODS AND COMPOSITIONS  
FOR THE TREATMENT OF  
PANCREATITIS

Commissioner for Patents  
Alexandria, VA 22313-1450

Certificate  
OCT 22 2004  
of Correction

REQUEST FOR  
CERTIFICATE OF CORRECTION  
UNDER RULE 322 (OFFICE MISTAKE)

Dear Sir:

Please correct the above-identified patent as shown on the accompanying Certificate of Correction Form PTO-1050.

These corrections are requested for the following reasons:

IN THE SPECIFICATION:

Column 12, line 36 (page 25, line 9); delete

"SYIANKVLTVTIDNALS KRNEKWDEVYKYIVTNWLAKVNTQIDLIRKKMF EAL ENQA" and  
insert in place thereof

--SYIANKVLTVTIDNALS KRNEKWDEVYKYIVTNWLAKVNTQIDLIRKKMKEAL ENQA --

Column 12, line 54 (page 25, line 19); delete

"QLFNLESSLIEVILKNAIVYNSMYENFSTSFWIRIPKYFNSISLNNEYTIINCMENNS"  
and insert in place thereof

--QLFNLESSKIEVILKNAIVYNSMYENFSTSFWIRIPKYFNSISLNNEYTIINCMENNS --

OCT 25 2004

Column 12, line 62 (page 25, line 23); delete

"NIYLNSSLYRGTKFIIKKYASGNKDNIVRNNDRVYINVVKKEYRLATNASQAGVEK"

and insert in place thereof

--NIYLNSSLYRGTKFIIKKYASGNKDNIVRNNDRVYINVVVKKEYRLATNASQAGVEK--

Column 15, line 25 (page 27, line 5); after " ataaaaaat atgcttctgg aaataaagat aatattgta gaaataatga tcgtgtatat"  
insert --attaatgtag tagttaaaaa taaagaatat aggttagcta ctaatgcac acaggcaggc--

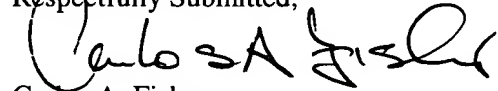
IN THE CLAIMS:

Column 36, lines 7 and 8, claim 18; (page 4 of amendment filed 12/22/03); delete "binge" and insert in place thereof --hinge--

Please send the Certificate to:

Allergan, Inc.  
Carlos A. Fisher (T2-7H)  
Intellectual Property Dept.  
2525 Dupont Drive  
Irvine, CA 92612

Respectfully Submitted,



Carlos A. Fisher  
Registration No. 36,510  
Telephone: 714/246-4920  
Telecopier: 714/246-4249

Allergan, Inc.  
2525 Dupont Drive  
Irvine, CA 92612

CERTIFICATE OF MAILING

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST-CLASS MAIL WITH SUFFICIENT POSTAGE IN AN ENVELOPE ADDRESSED TO THE: CERTIFICATE OF CORRECTION-NON FEE; COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450 ON 10/13/2004 Printed Name of Person Making Deposit:

Bonnie Ferguson; Signature of Person Making Deposit; Bonnie Ferguson  
Date: 10/13/2004

OCT 25 2004

**UNITED STATES PATENT AND TRADEMARK OFFICE**  
**CERTIFICATE OF CORRECTION**

Page 1 of 2

PATENT NO: 6,776,990 B2

DATED: August 17, 2004

INVENTORS: Sachs et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

IN THE SPECIFICATION:

Column 12, line 36; delete

“SYIANKVLT TVQTIDNALS KRNEKWDEVYKYIVTNWLAKVNTQIDLIRKKMFEALENQA”

and insert in place thereof

--SYIANKVLT TVQTIDNALS KRNEKWDEVYKYIVTNWLAKVNTQIDLIRKKMKEALENQA --

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and insert in place thereof

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Column 15, line 25; after " ataaaaaat atgcttctgg aaataaagat aatattgtta gaaataatga tcgtgtatat"  
insert --attaatgtag tagttaaaaa taaagaatat aggttagcta ctaatgcac acaggcaggc--

MAILING ADDRESS OF SENDER: Carlos A. Fisher (T2-7H) 17282(BOT)  
Allergan, Inc.  
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Irvine, CA 92612

PATENT NO. 6,776,990 B2

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Also Form PTO-1050

**UNITED STATES PATENT AND TRADEMARK OFFICE**  
**CERTIFICATE OF CORRECTION**

Page 2 of 2

PATENT NO: 6,776,990 B2

DATED: August 17, 2004

INVENTORS: Sachs et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

IN THE CLAIMS:

Column 36, lines 7 and 8, claim 18; delete "binge" and insert in place thereof --hinge--

MAILING ADDRESS OF SENDER: Carlos A. Fisher (T2-7H) 17282(BOT)  
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Column 36, lines 7 and 8, claim 18; delete "binge" and insert in place thereof --hinge--

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person of skill in the art. It is well known that the clostridial neurotoxins have three functional domains analogous to the three elements of the present invention. For example, the BoNT/A neurotoxin light chain is present in amino acid residues 1-448 of the BoNT/A prototoxin (i.e., before nick-

12

ing of the prototoxin to form the disulfide-linked dichain holotoxin); this amino acid sequence is provided below as SEQ ID NO: 7. Active site residues are underlined:

BoNT/A Light Chain (SEQ ID NO:7)

MPFVNKQFNYKDPVNGVDIAYIKIPNAGQMPPVKAFAKIHNKIWW  
I PERDTFTNPEEGDLNPPPEAKQVPVSYDSTYLSTDNEKDNYLKGVTKLFERIYSTD  
LGRMLLTSIVRGIPFWGGSTIDTELKVIDTNCINVIQPDGSYRSEELNLVIIGPSADI  
IQFECKSFGHEVLNLTRNGYGSTQYIRFSPDFTFGFEESLEVDTNPLLGAAGKATDPA  
VTLAHELIIHAGHRLYGIAINPNRVFKVNTNAYYEMSGLEVSFEELRTFGGHDAKPID  
LQENEFRLYYNFKFDIASTLNKAKSIVGTTASLQYMKNVFKEKYLLEDTSGRKFSVD  
KLKFDKLYKMLTEIYTEDNFVKFFKVLNRGTYNLNFDAVFKINIVPKVNYTIYDGFNL  
RNTNLAANFNGQNTTEINNMNFTKLKNFTGLFEFYKLLCVRGIITSKTKSLDRGYNK;

25 The heavy chain N-terminal ( $H_N$ ) translocation domain is contained in amino acid residues 449-871 of the BoNT/A amino acid sequence, shown below as SEQ ID NO: 8; a gated ion channel-forming domain probably essential for the translocation activity of this peptide is underlined (see Oblati-Montal et al., *Protein Sci.* 4:1490-1497(1995), hereby incorporated by reference herein.

ALNDLCIKVNNWDLFFSPSEDNFTNDLNKGEEITSDTNIEAAEENISLDLIQQYYLTFNF  
DNEPENISIEENLSSDIIGQLELMPNIEFFNGKKYELDKYTMFHYLRAQEFHGKRSI  
ALTNSVNEALLNPSRVYTFSSDYVKVKNKATEAAMFLGWVEQLVYDFTDETSEVSTT  
DKIADITIIIPYIGPALNIGNMLYKDDFVGALIFSGAVILLEFIPEIAIPVLGTFALV  
SYIANKVLTVOITIDNALSKRNEKWDEVYKYIVTNWLAKVNYQIDLIRKQFEEALENQA  
EATKAIINYQYNYTEEEKNNINFNIDDLSSKLNESINKAMININKFLNQCSVSYLMN  
SMIPYGVKRLDFDASLKDALLKYIYDNRGTLLIGQVDRLLKDKVNNLTSLDIPFQLSKY  
VDNQRLSTFTYIK;

45 The heavy chain C-terminal neural cell binding domain is contained in amino acid residues 872-1296 (SEQ ID NO: 9) of the BoNT/A prototoxin.

NIINTSILNRLYESNHLIDLRYASKINIGSKVNFDPIDKNQI  
QLFNLESLEIVILKNAIVNSMYENFSTSFWIRIPKYFNSISLNNEYTIINCMENNS  
GKWVSLNYGEIIWTLQDTQEIQRVVFYKYSQMINISDYINRWIFVTITNRLNLSKIY  
INGRLIDQKPISNLGNTHASNNIMFKLDGCRDTHRYIWIYFNLFDKELNEKEIKDLY  
DNQSNSGILKDFWGDYLYDKPYMYMLNLYDPNKYVDVNNVGIRGYMYLKGPRGSVMTT  
NIYLNSSLYRGTKFIIKKYASGNKDNIVRNNDRVYINVKNEYRLATNASQAGVER  
ILSALEIPDVGNLSQVVVMKSKNDQGITNCKMNLQDNNNGNDIGFIGHQFNNAKLK  
ASNWYNRQIERSSRTLGCSEWFI PVDDGWGERPL

65 The amino acid sequence of the BoNT/A prototoxin is encoded by nucleotides 358 to 4245 of the neurotoxin cDNA sequence, set forth herein below as SEQ ID NO: 10.

5 ALNDLCIKVNNWDLFFSPSEDNFTNDLNKGEEITSDTNIEAAEENISLDLIQQYYLTFNF  
 DNEPENISIIENLSSDIIGQLELMPNIERFPNGKKYELDKYTMFHYLRAQEFEGHKSRI  
 ALTNSVNEALLNPSRVYTFSSDYVKKVNKATEAAMFLGWVEQLVYDFTDETSEVSTT  
 DKIADITIIIPYIGPALNIGNMLYKDDFVGALIFSGAVILLEFIPEIAIPVLGTFALV  
 SYIANKVLTVQTIDNALSkrNEKWDEVYKYIVTNWLAKVNTQIDLIRKKMKEALENQA X  
 10 EATKAIINYQYNQYTEEEKNNINFNIDDLSSKLNESINKAMININKFLNQCSVSYLMN  
 SMIPYGVKRLEDFDASLKDALLKYIYDNRGTLIGQVDRLKDKVNNTLSTDIPFQLSKY  
 VDNQRLSTFTTEYIK;

The heavy chain C-terminal neural cell binding domain  
 15 is contained in amino acid residues 872-1296 (SEQ ID NO: 9)  
 of the BoNT/A prototoxin.

NIINTSILNRLYESNHLIDLSRYASKINIGSKVNFDPIDKNQI  
 QLFNLESSKIEVILKNAIVYNSMYENFSTSWIRIPKYFNSISLNNEYTIINCMENNS X  
 20 GWKVS LN YGEI IWT LQDTQEIKQ RVVFKYSQMINISDYINRWIFVTITNNRLNNSKIY  
 INGR LIDQKPISNLGNIHASNNIMFKLDGCRDTHRYIWI KYFNLFDKELNEKEIKDLY  
 DNQNSGILKDFWGDYLQYDKPYMLNLYDPNKYVDVNNYGIRGYMYLKGPRGSVMTT  
 NIYLNSSLYRGTKFIIKKYASGNKDNIVRNNDRVYINVVKNKEYRLATNASQAGVEK X  
 ILSALEIPDVGNLSQVVVMKSKNDQGITNKCKMNLQDNNNGNDIGFIGFHQFNNI AKLV  
 25 ASNWYNRQIERSSRTLGCSEWEIFVDDGWGERPL

The amino acid sequence of the BoNT/A prototoxin is encoded  
 by nucleotides 358 to 4245 of the neurotoxin cDNA sequence,  
 set forth herein below as SEQ ID NO: 10.

30 |  
 aagcttctaa atttaaatta ttaagtataa atccaaataa acaatatgtt caaaaacttg  
 atgaggtaat aatttctgta ttagataata tggaaaaata tatagatata tctgaagata  
 atagattgca actaatagat aacaaaaata acgcaaagaa gatgataatt agtaatgata  
 tatttatttc caattgttta accctatctt ataacggtaa atatatatgt ttatctatga  
 35 aagatgaaaa ccataattgg atgatatgta ataatgatat gtcaaagtat ttgtatttat  
 ggtcatttaa ataattaata atttaattaa ttttaaatat tataagaggt gttaaatatg  
 ccatttgtaa ataaacaatt taattataaa gatcctgtaa atgggtgttg tattgcttat  
 ataaaaattc caaatgcagg acaaatgcaa ccagtaaaag cttttaaaat tcataataaa  
 atatgggtta ttccagaaag agatacattt acaaatcctg aagaaggaga tttaaattcca  
 40 ccaccagaag caaaacaagt tccagtttca tattatgatt caacatattt aagtacagat  
 aatgaaaaag ataattattt aaagggagtt acaaaattat ttgagagaat ttattcaact  
 gatcttggaa gaatgttggt aacatcaata gtaaggggaa taccattttg ggggtggaagt  
 acaatagata cagaattaaa agttattgat actaattgta ttaatgtgat acaaccagat  
 ggtagttata gatcagaaga acttaattcta gtaataatag gaccctcagc tgatattata  
 45 cagtttgaat gtaaaagctt tggacatgaa gttttgaatc ttacgcgaaa tggttatggc  
 tctactcaat acattagatt tagccagat tttacatttg gttttgagga gtcacttgaa

-continued

gtatcatata ttgcgaataa ggttctaacc gttcaacaa tagataatgc tttaagtaaa  
 agaaatgaaa aatgggatga ggtctataaa tatatagtaa caaattgggt agcaaagggt  
 aatacacaga ttgatctaata aagaaaaaaa atgaaagaag ctttagaaaa tcaagcagaa  
 gcaacaaagg ctataataaa ctatcagtat aatcaatata ctgaggaaga gaaaaataat  
 attaatTTTA atattgatga tttaagttcg aaacttaatg agtctataaa taaagctatg  
 attaatataa ataaattttt gaatcaatgc tctgtttcat atttaatgaa ttctatgac  
 ccttatgggt ttaaaccggt agaagatttt gatgctagtc ttaaagatgc attattaaag  
 tatatatatg ataatagagg aactttaatt ggtcaagtag atagattaaa agataaagtt  
 aataatacac ttagtacaga tatacctttt cagctttcca aatacgtaga taatcaaaga  
 ttattatcta catttactga atattattaag aatattatta atacttctat attgaattta  
 agatatgaaa gtaatcattt aatagactta tctaggtatg catcaaaaat aaatattggt  
 agtaaagtaa attttgatcc aatagataaa aatcaaattc aattatttaa tttagaaagt  
 agtaaaattg aggtaatTTT aaaaaatgct attgtatata atagtatgta tgaaaatttt  
 agtactagct ttggataag aattcctaag tattttaaca gtataagtct aaataatgaa  
 tatacaataa taaattgtat ggaaaaataat tcaggatgga aagtatcact taattatggt  
 gaaataatct ggactttaca ggatactcag gaaataaaac aaagagtagt ttttaatac  
 agtcaaatga ttaatatatc agattatata aacagatgga ttttgtaac taccactaat  
 aatagattaa ataactctaa aatttatata aatggaagat taatagatca aaaaccaatt  
 tcaaatttag gtaatatcca tgctagtaat aatataatgt ttaaattaga tggttgtaga  
 gatacacata gatattttg gataaaatat tttaatcttt ttgataagga attaaatgaa  
 aaagaaatca aagatttata tgataatcaa tcaaattcag gtattttaaa agacttttgg  
 ggtgattatt tacaatatga taaaccatac tatatgttaa atttatatga tccaaataaa  
 tatgtcgatg taaataatgt aggtattaga gggttatgt atcttaagg gcctagaggt  
 agcgtaatga ctacaaacat ttatttaaat tcaagtttgt atagggggac aaaatttatt  
 ataaaaaat atgcttctg aaataaagat aatattgtta gaaataatga tctgttatat  
 gtgaaaaaa tactaagtgc attagaaata cctgatgtag gaaatctaag tcaagtagta  
 gtaatgaagt caaaaaatga tcaaggaata acaataaaat gcaaaatgaa tttacaagat  
 aataatggga atgatatagg ctttatagga ttcatcagt ttaataatat agctaaacta  
 gtacgaagta attggtataa tagacaaata gaaagatcta gtaggacttt gggttgctca  
 tgggaattta ttctgtaga tgatggatgg ggagaaaggc cactgtatatt aatctcaaac  
 tacatgagtc tgtcaagaat ttctgttaa catccataaa aattttaaaa ttaatatgtt  
 taagaataac tagatatgag tattgtttga actgcccctg tcaagtagac aggtaaaaaa  
 ataaaaatta agataactatg gtctgatttc gatattctat cggagtcaga ccttttaact  
 ttctttgtat cctttttgta ttgtaaaact ctatgtattc atcaattgca agttccaatt  
 agtcaaaatt atgaaacttt ctaagataat acatttctga ttttataatt tcccaaaatc  
 cttccatagg accattatca atacatctac caactcgaga catactttga gttgcgcta  
 ttctattaag tttattcttg aaagatttac ttgtatattg aaaaccgcta tcaactgtgaa  
 aaagtggact agcatcagga ttggaggtaa ctgctttatc aaaggtttca aagacaagga  
 cgttgttatt tgattttcca agtacatagg aaataatgct attatcatgc aaatcaagta  
 tttcactcaa gtacgccttt gtttcgtctg ttaac

insert  
 X missing line

*missing on  
issued patent*

5 attaatgtag tagttaaaaa taaagaatat aggttagcta ctaatgcatac acaggcaggc  
 gtagaaaaaa tactaagtgc attagaaata cctgatgtag gaaatctaag tcaagtagta  
 gtaatgaagt caaaaaatga tcaaggaata acaataaat gcaaaatgaa tttaacaagat  
 aataatggga atgatatagg ctttatagga ttcatcagt ttaataatat agctaaacta  
 gtagcaagta attggtataa tagacaaata gaaagatcta gtaggacttt gggttgctca  
 10 tgggaattta ttctgtaga tgatggatgg ggagaaaggc cactgtaatt aatctcaaac  
 tacatgagtc tgtcaagaat ttctgtaaa catccataaa aattttaaaa ttaatattgtt  
 taagaataac tagatatgag tattgtttga actgccctg tcaagtagac aggtaaaaaa  
 ataaaaatta agatactatg gtctgatttc gatattctat cggagtcaga ccttttaact  
 tttcttgtat cctttttgta ttgtaaaact ctatgtattc atcaattgca agttccaatt  
 15 agtcaaaatt atgaaacttt ctaagataat acatttctga tttataatt tcccaaaatc  
 cttccatagg accattatca atacatctac caactcgaga catactttga gttgcgcta  
 tctcattaag ttatttcttg aaagatttac ttgtatattg aaaaccgcta tcaactgtgaa  
 aaagtggact agcatcagga ttggaggtaa ctgctttatc aaaggtttca aagacaagga  
 cgttgttatt tgattttcca agtacatagg aaataatgct attatcatgc aaatcaagta  
 20 tttcactcaa gtacgccttt gtttcgtctg ttaac

Of course, three distinct domains analogous to those  
 described above for BoNT/A exist for all the BoNT subtypes  
 as well as for TeNT neurotoxin; an alignment of the amino  
 25 acid sequences of these holotoxins will reveal the sequence  
 coordinates for these other neurotoxin species.

Preferably, the translocation element and the binding  
 element of the compositions of the present invention are  
 separated by a spacer moiety that facilitates the binding  
 30 element's binding to the desired cell surface receptor. Such  
 a spacer may comprise, for example, a portion of the BoNT Hc  
 sequence (so long as the portion does not retain the ability  
 to bind to motor neurons or sensory afferent neurons),  
 another sequence of amino acids, or a hydrocarbon moiety.  
 35 The spacer moiety may also comprise a proline, serine,  
 threonine and/or cysteine-rich amino acid sequence similar  
 or identical to a human immunoglobulin hinge region. In a  
 preferred embodiment, the spacer region comprises the amino  
 acid sequence of an immunoglobulin  $\gamma 1$  hinge region; such a  
 40 sequence has the sequence (from N terminus to C terminus):

35

8. The composition of claim 5 wherein said binding element comprises an amino acid sequence consisting of SEQ ID NO: 6.

9. The composition of claim 8 wherein said binding element comprises an amino acid sequence consisting of SEQ ID NO: 5.

10. The composition of claim 9 wherein said binding element comprises an amino acid sequence consisting of SEQ ID NO: 4.

11. The composition of claim 10 wherein said binding element comprises an amino acid sequence consisting of SEQ ID NO: 3.

12. The composition of claim 11 wherein said binding element comprises an amino acid sequence consisting of SEQ ID NO: 2.

13. The composition of claim 1 wherein said composition further comprises a spacer moiety separating said binding element from said translocation element.

14. The composition of claim 13 wherein said spacer moiety comprises a moiety selected from the group consisting of a hydrocarbon, a polypeptide other than an immunoglobulin hinge region, and a proline-containing polypeptide identical or analogous to an immunoglobulin hinge region.

15. The composition of claim 14 wherein said spacer moiety comprises a proline-containing polypeptide identical or analogous to an immunoglobulin hinge region.

16. The composition of claim 15 wherein said polypeptide comprises an amino acid sequence consisting of SEQ ID NO: 11.

36

17. The composition of claim 7 wherein said composition further comprises a spacer moiety separating said binding element from said translocation element.

18. The composition of claim 17 wherein said spacer moiety comprises a moiety selected from the group consisting of a hydrocarbon, a polypeptide other than an immunoglobulin hinge region, and a proline-containing polypeptide identical or analogous to an immunoglobulin hinge region.

19. The composition of claim 18 wherein said spacer moiety comprises a proline-containing polypeptide identical or analogous to an immunoglobulin hinge region.

20. The composition of claim 19 wherein said polypeptide comprises an amino acid sequence consisting of SEQ ID NO: 11.

21. The composition of claim 8 wherein said composition further comprises a spacer moiety separating said binding element from said translocation element.

22. The composition of claim 17 wherein said spacer moiety comprises a moiety selected from the group consisting of a hydrocarbon, a polypeptide other than an immunoglobulin hinge region, and a proline-containing polypeptide identical or analogous to an immunoglobulin hinge region.

23. The composition of claim 18 wherein said spacer moiety comprises a proline-containing polypeptide identical or analogous to an immunoglobulin hinge region.

24. The composition of claim 19 wherein said polypeptide comprises an amino acid sequence consisting of SEQ ID NO: 11.

\* \* \* \* \*

17. (Original) The composition of claim 7 wherein said composition further comprises a spacer moiety separating said binding element from said translocation element.
18. (Original) The composition of claim 17 wherein said spacer moiety comprises a moiety selected from the group consisting of a hydrocarbon, a polypeptide other than an immunoglobulin hinge region, and a proline-containing polypeptide identical or analogous to an immunoglobulin hinge region. X
19. (Original) The composition of claim 18 wherein said spacer moiety comprises a proline-containing polypeptide identical or analogous to an immunoglobulin hinge region. X
20. (Original) The composition of claim 19 wherein said polypeptide comprises an amino acid sequence consisting of SEQ ID NO:11.
21. (Original) The composition of claim 8 wherein said composition further comprises a spacer moiety separating said binding element from said translocation element.
22. (Original) The composition of claim 17 wherein said spacer moiety comprises a moiety selected from the group consisting of a hydrocarbon, a polypeptide other than an immunoglobulin hinge region, and a proline-containing polypeptide identical or analogous to an immunoglobulin hinge region.
23. (Original) The composition of claim 18 wherein said spacer moiety comprises a proline-containing polypeptide identical or analogous to an immunoglobulin hinge region.
24. (Original) The composition of claim 19 wherein said polypeptide comprises an amino acid sequence consisting of SEQ ID NO:11.

25-50 (Cancelled)